TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

Protecting Texas by Reducing and Preventing Pollution

November 3, 2011

Ms. Danica Andrews
National Institute of Environmental Health Sciences
P.O. Box 12233, MD K2–03
Research Triangle Park, NC 27709

Re: Draft NTP Monograph on Health Effects of Low-Level Lead

Dear Ms. Andrews:

The Texas Commission on Environmental Quality (TCEQ) appreciates the opportunity to respond to the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services (DHHS) announcement of a public comment period published in the October 5, 2011, edition of the *Federal Register* entitled: "Draft NTP Monograph on Health Effects of Low-Level Lead."

Enclosed, please find TCEQ's detailed comments relating to the DHHS action referenced above. If you have comments or questions concerning the enclosed comments, please contact Gulan Sun, Ph.D., Toxicology Division, Chief Engineer's Office, (512) 239-1336 or gulan.sun@tceq.texas.gov.

Sincerely,

Redacted

Mark R. Vickery, P.G.
Executive Director

Enclosure

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Texas Commission on Environmental Quality (TCEQ) Comments to the National Toxicology Program (NTP), U.S. Department of Health and Human Services, on the Draft NTP Monograph on Health Effects of Low-Level Lead

On October 5, 2011, the National Toxicology Program (NTP) of the U.S. Department of Health and Human Services (DHHS) published a Federal Register notice (76 *Federal Register* 61705) announcing a public comment period (ending Nov 3, 2011) for the "Draft NTP Monograph on Health Effects of Low-Level Lead" (hereafter called Draft NTP Monograph) which indicated that the Draft NTP Monograph would be made available on October 14, 2011. The Texas Commission on Environmental Quality (TCEQ) has developed comments on the Draft NTP Monograph to the extent practicable in the short time allotted by DHHS.

General Comments

The DHHS's request for comment on the Draft NTP Monograph is unreasonable given the short comment period being allowed by DHHS for review.

The assessment of the health effects associated with low-level lead exposure has great implications in a regulatory context. However, a comment period of less than three weeks from the time the document is made available is insufficient for regulatory agencies and others to provide the most thorough and meaningful comments possible based on an in-depth review and analysis of the Draft NTP Monograph. There is great complexity associated with multiple issues relevant to the assessment of health effects of lead, especially at low exposure levels. Given the complexity and volume of relevant materials, it is impracticable for DHHS to expect detailed specific comments from external experts in the short period allowed for a critical review of the Draft NTP Monograph. The 20-day comment period allows only a superficial review of the Draft NTP Monograph at best, leads to a less-than-desirable level of transparency and peer review, and undermines confidence in the process. Consequently, TCEQ is only able to provide comments based on a cursory review. If *DHHS* seeks more detailed and meaningful public input and technical comments, at a minimum *DHHS* should extend the comment period at least 60 days past the current deadline to allow stakeholders to: (1) perform a more detailed review of the volumes of relevant information; (2) more fully examine statistical procedures and the rationale and scientific support for key DHHS decisions and analyses; and (3) provide more detailed specific comments on all problematic issues associated with the Draft NTP Monograph.

Comments on Health Effects of Low-Level Lead

The TCEQ disagrees with the NTP conclusion and strongly believes that some key studies used by DHHS in the Draft NTP Monograph are inadequate to demonstrate sufficient evidence of an association between blood Pb levels < 5 μg/dL in children and decreased academic performance, and increased incidence of attention deficit hyperactivity disorder (ADHD).

Sufficient evidence of an association has been defined in the Draft NTP Monograph as an observed relationship between the exposure and health outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. However, some key studies used by DHHS in the Draft NTP Monograph are inadequate to demonstrate sufficient evidence of an association between blood Pb levels < 5 μg/dL in children and decreased academic performance, and increased incidence of ADHD.

- **Academic performance**

Two studies (Miranda et al. 2007, 2009) have been cited in the Draft NTP Monograph to demonstrate that blood Pb levels down to 2 μg/dL were negatively related to test performance in both reading and mathematics.

Miranda et al. (2007) linked blood Pb surveillance data collected between 0 and 5 years with end-of-grade testing data for the 4th grade and found that for both reading and math, achievement test scores were inversely associated with early childhood blood Pb screening data. However, as stated in the paper, white children were overrepresented in the lower blood Pb level categories (blood Pb level 1 to 3 μg/dL) and underrepresented in the higher blood Pb level categories (blood Pb level 4 to ≥ 10 μg/dL). The referent group (blood Pb 1 μg/dL) was defined by the investigator as white female students who do not participate in the free or reduced cost lunch program, which could have contributed to the finding of lower 4th grade end-of-grade scores in children with a blood Pb of 2μg/dL who were proportionally more socioeconomically disadvantaged, an important confounding factor when comparing academic performance between groups that was not accounted for. A subsequent larger study by Miranda et al. (2009) revealed that parental educational differences accounted for the largest part of the test score decrement at any percentile (58–65% of total decrement), with participation in the lunch program being second and accounting for 25-28% of the test score decrement, as opposed to Pb exposure (effects of increased blood Pb from 1 to 5 μg/dL) accounting for only 7-16%. Thus, Miranda et al. (2009) found that indicators of socioeconomic status (i.e., parental education and enrollment in a free/reduced fee lunch program) accounted for the vast majority of score decrement (83-93%), and interpretation of poor academic performance due to blood Pb levels as low as 2 μg/dL in children is not scientifically defensible, at least in these two studies.

The Draft NTP Monograph states it supports EPA's 2011 draft Integrated Science Assessment (ISA) for Lead (EPA 2011a):

> NTP's conclusions for sufficient evidence that decreased academic achievement in children aged 6-18 is associated with Pb levels < 5 μg/dL, extend the conclusions from EPA's 2006 AQCD for Lead and ATSDR's 2007 Toxicological Profile for Lead which were limited to blood Pb levels <10μg/dL; however, the EPA's 2011 draft (USEPA 2011a) currently supports a lower blood Pb level.

EPA concluded in its draft ISA for lead (EPA 2011a) that poor academic performances are causally associated with blood Pb levels as low as 2 μg/dL in children, based, in part, on the studies of Miranda et al.(2007, 2009). However, EPA (2011b) states in its Risk and Exposure Assessment Planning Document from the summary of the draft ISA for lead:

> The extent to which the evidence provides strong support for a quantitative characterization of the concentration-response relationship for non-IQ behavioral (including academic performance and ADHD) endpoints is unclear.

TCEQ agrees with the above EPA conclusion that any quantitative concentration-response relationship between blood Pb levels and poor academic performance and/or ADHD in children is unclear (EPA 2011b). Thus, this unclear relationship should not be used in a quantitative manner to support any given regulatory or other action (e.g., lowering the blood Pb level of concern to a particular value).

- **ADHD**

The Draft NTP Monograph concluded:

> In children, there is **sufficient** evidence that blood Pb levels < 5 μg/dL are associated with increased diagnosis of attention deficit hyperactivity disorder (ADHD), greater incidence of problem behaviors, and decreased cognitive performance as indicated by lower academic achievement and specific cognitive measures [emphasis added].

> Increased diagnosis of ADHD and ADHD-related behaviors such as inattention and hyperactivity are consistently reported in studies with mean blood Pb levels < 5 µg/dL and in several studies at blood Pb levels < 2 µg/dL.

However, associations are not necessarily conclusive. A specific example regarding an inconclusive association between blood lead at 2 µg/dL and ADHD using the National Health and Nutrition Examination Survey (NHANES) data is in the Draft NTP Monograph. While NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States, a recent analysis of NHANES 1999-2002 data cited by the Draft NTP Monograph (Braun et al. 2006) found a positive relationship between blood lead level and ADHD (parental reporting of a diagnosis of ADHD or use of stimulant medication). However, the associations were not statistically significant. Using the same NHANES dataset, restricting children ages to 8-15 years, Froehlich et al. (2009) (also cited in the draft NTP Monograph) found that although both prenatal tobacco smoke (maternal report) exposure and blood lead levels are associated with ADHD, prenatal tobacco smoke exposure was the greater risk factor. However, both studies have an important limitation because of their inability to adjust for parental psychopathology - one of the most important confounders for studying the associations of ADHD and environmental risk factors since ADHD heritability has been estimated to be about 75% (Biederman and Faraone 2005, Aguiar et al. 2010). Therefore, for diseases or health effects with a complex etiology such as ADHD or learning and IQ deficits, many confounders (currently both known and unknown) have to be considered and carefully adjusted for when attempting to elucidate any association, statistical or causal, between blood Pb levels and diseases or health effects. Without such adjustments, as with these ADHD studies, DHHS simply cannot rule out confounding with reasonable confidence for a finding of sufficient evidence.

Since Pb was phased out in paint, solder, and gasoline in the United States, the blood Pb concentrations in children have declined significantly. Blood Pb levels in young children (ages 1-5 years) have decreased 10-fold over the last 30 years from a geometric mean of 15.1 µg/dL in 1976-1980 to 1.51 µg/dL in 2007-2008 (CDC 2007, 2011). However, according to the CDC, rates of ADHD diagnoses have increased an average of 3% per year from 1997 to 2006 and an average of 5.5% per year from 2003 to 2007. Significant decreases in child blood Pb levels are inconsistent with concurrent increases in the prevalence of ADHD if Pb exposure plays any appreciable role in ADHD.

The TCEQ disagrees with the NTP conclusion and strongly believes that the key study utilized by DHHS in the Draft NTP Monograph is inadequate to demonstrate sufficient evidence of an association between blood Pb levels < 10 µg/dL in children and decreased IQ.

- **IQ**

The Lanphear et al. (2005) pooled analysis is cited as a key study in the Draft NTP Monograph for a decline up to six full-scale IQ points for an increase in blood Pb from 1 to 10 µg/dL in children. However, the concentration and response between blood Pb levels < 10 µg/dL and IQ loss in the study (Lanphear et al. 2005) was estimated using models, not actual observations. Thus, any resulting conclusions are based on uncertain modeling results, not actual data points within the blood Pb range of interest. The Draft NTP Monograph acknowledges that many of the cross-sectional and prospective studies included in the key meta-analyses (Lanphear et al. 2005) are based on studies with blood Pb levels >10µg/dL at some age from birth to evaluation of IQ. Specifically, the geometric means of concurrent blood levels and peak blood lead levels in studying children population were 9.7 and 18 µg/dL, respectively (Lanphear et al. 2005). Of the study population, the percentage of children with the peak blood lead concentration < 10 µg/dL and 7.5 µg/dL are 18.3 % and 7.7%, respectively. EPA (2011b) states in its Risk and Exposure Assessment Planning Document.

> Uncertainty associated with the magnitude of IQ loss predicted for simulated children, particularly at lower total blood Pb levels (e.g., < 2.5 μg/dL) reflects the appreciably less extensive information available on which to base our characterization of the concentration-response function at lower blood Pb levels. The varied studies on associations between IQ and blood Pb now available do not provide a strong foundation for development of a new or adjusted concentration response function.

Thus, EPA acknowledges appreciable uncertainty due to a less-than-desirable level of information in modeling concentration-response at low doses, and a weak foundation for development of a new or adjusted concentration-response function. In addition, a recently published study by Ramsden et al. (2011) indicated an individual's intellectual capacity relative to their peers can decrease or increase in the teenage years, indicating that IQ fluctuates.

For the reasons discussed above, the TCEQ disagrees with the NTP conclusion as the key study utilized by DHHS in the Draft NTP Monograph is inadequate to demonstrate sufficient evidence of an association between blood Pb levels < 10 μg/dL in children and decreased IQ.

The TCEQ disagrees with the NTP conclusion and strongly believes that concurrent blood Pb levels are an inappropriate lead exposure metric for studies of chronic health effects in adults, and thus fail to support that blood Pb levels <5 μg/dL are associated with decreased renal function and that blood Pb levels <10 μg/dL are associated with increased blood pressure, hypertension, and increased cardiovascular-related mortality in adults.

- **Use of Concurrent Blood Pb Levels as an Exposure Metric**

The Draft NTP Monograph concluded:

> In adults, epidemiological data provide **sufficient** evidence that blood Pb levels < 5 μg/dL are associated with decreased renal function and blood Pb levels < 10 μg/dL are associated with increased blood pressure, hypertension, and increased cardiovascular-related mortality [emphasis added].

However, use of concurrent blood Pb levels as the exposure metric may preclude a conclusion of "sufficient evidence of an association" in the draft NTP Monograph. There is uncertainty associated with using concurrent blood Pb levels as an exposure metric for studies of chronic health effects in adults, which has also been emphasized many times by DHHS in its own Draft NTP Monograph.

> Epidemiological data from the general population support an association with concurrent blood Pb levels; however, the potential effect of early-life blood Pb levels on kidney function in adults cannot be discriminated from the effect of concurrent blood Pb levels without additional prospective studies in a population for which blood Pb levels remain consistently below 10μg/dL from birth until evaluation of kidney function.

Prior to bans on Pb in paint, solder, and gasoline, environmental Pb levels in the United States were higher. The majority of US children born before 1980 had blood Pb levels > 10 μg/dL during early childhood. Consequently, health effects in adults today may have been influenced by blood Pb levels > 10 μg/dL that many individuals experienced earlier in life, precluding any confident conclusions based on concurrent levels.

EPA (2011b) stated in its Risk and Exposure Assessment Planning Document that the contribution to blood lead from endogenous Pb (e.g., stored in bone) that can reflect historical Pb exposures complicates the utilization of blood lead as a biomarker of current exposures in adults, and consequently contributes uncertainty in interpreting epidemiological studies with regard to the Pb exposures eliciting observed health outcomes. Therefore, given the uncertainty surrounding use of concurrent blood Pb levels as a lead exposure metric for studies of chronic health effects in adults, epidemiological data may not be likely to provide sufficient evidence that blood Pb levels < 5 µg/dL are associated with decreased renal function. Likewise, epidemiological data may not be likely to provide sufficient evidence that blood Pb levels < 10 µg/dL are associated with increased blood pressure, hypertension, and increased cardiovascular-related mortality in adults.

The TCEQ generally agrees with the exposure metric that bone Pb is a better measure of the cumulative body burden of Pb and may show more consistent associations with long-term health outcomes in the Draft NTP Monograph.

While Pb can be measured in a variety of human tissues, whole blood Pb is the most common measure used in both research and clinical settings. Blood Pb levels fluctuate and represent both current exogenous exposures and endogenous sources of Pb (i.e. primarily stored in bone from historical Pb exposures). For studies of chronic health effects, bone Pb is a better measure of the cumulative body burden of Pb and may show more consistent associations with long term health outcomes.

Summary

The TCEQ disagrees with the NTP conclusion and strongly believes that some key studies utilized by DHHS in the Draft NTP Monograph are inadequate to demonstrate sufficient evidence of an association between blood Pb levels < 5 µg/dL in children and decreased academic performance, and increased incidence of ADHD. Neurological effects such as poor academic performance, ADHD or IQ loss depend on a variety of factors. In such circumstances, epidemiology studies are significantly limited in their ability to accurately identify and quantify adverse effects and to control for potential confounding by non-Pb-exposure-related factors or variables such as parental IQ, socioeconomic status, parent education, alcohol/drug use and parental psychopathology. Consequently, when the health outcomes of concern have complex etiologies such that all important confounders are difficult to obtain data on and adjust for, as with Pb, a scientifically defensible and accurate dose-response assessment is unlikely.

The DHHS should acknowledge that the dramatic decreases in children's blood Pb levels are inconsistent with the suggestion that Pb is an appreciable factor in the increased frequency of ADHD (i.e., significant decreases in child Pb exposure are inconsistent with concurrent increases in the prevalence of ADHD).

The TCEQ disagrees with the NTP conclusion and strongly believes that concurrent blood Pb levels are an inappropriate lead exposure metric for studies of chronic health effects in adults, and thus fail to support the conclusion that blood Pb levels < 5 µg/dL are associated with decreased renal function and blood Pb levels < 10 µg/dL are associated with increased blood pressure, hypertension, and increased cardiovascular-related mortality in adults. Health effects in adults today may have been influenced by blood Pb levels > 10 µg/dL that many individuals experienced earlier in life, precluding any confident conclusions based on concurrent levels.

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